REMARKS

AMENDMENTS TO THE SPECIFICATION

The Title of the specification was amended to substitute the phrase "Identification and Cloning of a Full-length" with the phrase "Polynucleotides Encoding", in addition to substituting the term "Gene" with the term "Polypeptide". These amendments were made solely to address the Examiners objection to the same and to make the Title consonant with the claimed invention. Support for these amendments may be found in paragraph [0014] on page 5 of the specification, and in pending Claims 36 to 69. No new matter has been added.

STATUS OF THE CLAIMS

Claims 1 to 35 are cancelled.

Claims 52, 61, 62, and 65 were amended.

Claims 36 to 69 are pending.

Claim 52 was amended to make this claim independent by substituting the phrase "(a) or (b) of Claim 36" with the phrase "either an isolated polynucleotide encoding a polypeptide comprising amino acids 1 to 443 of SEQ ID NO:2, or an isolated polynucleotide encoding a polypeptide comprising amino acids 2 to 443 of SEQ ID NO:2" to overcome the Examiner's rejection of the same. No new matter has been added.

Claims 61 and 62 were amended to substitute the term "comprising" with the phrase "consisting of". Support for this amendment may be found in original Claims 1 and 11, wherein "amino acids 324 to 407 of SEQ ID NO:2" represents a "polypeptide consisting of...a polypeptide fragment of SEQ ID NO:2" (Claim 11(a)), and wherein "nucleotides 1289 to 1540 of SEQ ID NO:1" represents "a nucleic acid molecule consisting of...a polynucleotide fragment of SEQ ID NO:1" (Claim 1(a)).

Claim 65 was amended to append the phrase ", and wherein said polynucleotide encodes a polypeptide that binds to Grb2, Vav, Lat, c-Cbl or SLP-76" after the "single nucleotide substitution" phrase. Support for this amendment may be found in paragraphs [0051], [0157], and [0166], and throughout the specification as originally filed.

I. Miscellaneous

a. Substance of the Interview with Examiner Mertz on July 25, 2006

Applicants appreciate the Examiner's courtesy in discussing some of the pending claims during a telephonic interview on July 25, 2006. In supplement to the Examiner's Interview Summary submitted with the August 2, 2006 Office Action, Applicants note that Claims 55, 57, 59, 61, and 63 were discussed relative to the Grb2, Vav, Lat, c-Cbl, or SLP-76 binding activity under 35 U.S.C. § 112, first paragraph. Applicants pointed out that the Grb2, Vav, Lat, c-Cbl, or SLP-76 binding activity for each sequence embraced by these claims was adequately demonstrated in Figures 12, 13, and 14 via the SH2, PR, and/or phosphotyrosine domains contained within each sequence. The Examiner agreed.

b. Objections to the Specification

The Examiner objected to the Title of the specification stating:

> The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. It is suggested that the title of the invention be amended to recite "A nucleic acid encoding human Clnk-related gene, MIST (Mast Cell Immunoreceptor Signal Transducer)".

In response, Applicants have amended the Title to be consonant with the claimed invention.

Applicants believe all of the Examiner's objections to the specification have been overcome in consideration of this amendment.

c. Public Access to and Viability of ATCC Deposit No. PTA-2981

Applicants representative hereby gives the following assurance by signature below:

Bristol-Myers Squibb Company, an assignee of the present application, has deposited biological material under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209. The deposit comprises the cDNA sequence (referred to as hMIST Clone #8 encoding the human MIST (SEQ ID NO:2) polypeptide of the present invention. The deposit for human MIST was made on January 26, 2001, and given ATCC Accession Number PTA-2981. In accordance with MPEP 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all

restrictions on the availability to the public of ATCC Accession Number PTA-2981 for the human MIST clone will be irrevocably removed upon the grant of a patent based on the captioned application, except as permitted under 37 C.F.R. § 1.808(b).

Applicants representative also hereby gives the following additional assurance by signature below:

In accordance with 37 C.F.R. § 1.805 to § 1.807, assurance is hereby given that the viability of the deposit for human MIST, made on January 26, 2001, and given ATCC Accession Number PTA-2981, will be maintained during the pendency of the captioned application for a duration of at least 30 years or at least five years after the most recent request for the furnishing of a sample of the deposit is received by the ATCC, or whichever is longer; and that the deposit will be replaced if it should ever become unviable.

II. Rejections under 35 U.S.C. § 112 – First Paragraph - Enablement

a. The Examiner has rejected Claim 49 under 35 U.S.C. § 112, first paragraph, alleging these claims are not described in which a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention. More particularly, the Examiner alleges

> The deposit of biological material is considered by the Examiner to be necessary for the enablement of the current invention because the claims require availability of the deposit. Elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. When biological material is required to practice an invention, and if it is not so obtainable or available, the enablement requirements of 35 USC §l 12, first paragraph, may be satisfied by a deposit of the material. See 37 CFR 1.802.
>
> The specification does not provide a repeatable method for obtaining ATCC Deposit No. PTA-736 (sic) and it does not appear to be a readily available material. The ATCC® PTA-2981 deposit in full compliance with 37 CFR §§ 1.803-1.809 would satisfy the requirements of 35 USC §112, first paragraph.
>
> If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.
>
> If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or Declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record

over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the rammer described in the specification.

In the instant case, Applicants have made a deposit of PTA-2981. However, the statement submitted on 6/21/2006 fails to recite that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent".

A new statement reciting all the necessary criteria stated above is required to satisfy the deposit requirements. See 37 CFR 1.808.

In response, Applicants representative has provided the required assurance in the "Miscellaneous" section of Applicants Reply *supra*. Applicants believe the Examiners rejection of Claim 49 under 35 U.S.C. § 112, first paragraph has been overcome in consideration of Applicants assurances provided herein.

In the interest of correcting the record, Applicants note that ATCC deposit PTA-2981 is erroneously referred to as "PTA-736" in the above citation of the Examiner's August 2, 2006 office action. In addition, Applicants also note that no statement regarding ATCC deposit PTA-2981 was submitted in Applicants June 21, 2006 Preliminary Amendment. Rather, only a copy of the ATCC deposit receipt for ATCC deposit PTA-2981 was provided.

b. The Examiner has rejected Claims 47 to 48, and 65 to 69 under 35 U.S.C. § 112, first paragraph, alleging these claims are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. More particularly, the Examiner alleges

> The claims are drawn to an isolated nucleic acid having at least 95% sequence identity with a particular disclosed sequence (SEQ ID NO:I). The claims do not require that the polypeptide encoded by the nucleic acid possess any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids encoding polypeptides that is defined only by sequence identity. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of malting the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved for the biological activity of the polypeptide that binds Grb2, Vav, Lat, c-Cbl or SLP-76. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics and structure/function relationship, the specification does not provide adequate written description of the claimed genus of nucleic acid molecules. Similarly, the specification does not provide an adequate written description for a polynucleotide containing a single nucleotide substitution, which substitution can be in a conserved or a non-conserved nucleotide resulting in an amino acid substitution in the polypeptide of amino acid sequence set forth in SEQ ID NO:2.

Applicants disagree and assert that the instant specification does in fact contain the requisite teachings to convince a skilled artisan that Applicants were in possession of the genus encompassed by Claims 47 and 48. First, Applicants point out that Claims 47 and 48 do not merely define a genus according to sequence identity, rather, these claims also contain the functional limitation that the sequence binds to Grb2, Vav, Lat, c-Cbl or SLP-76. In addition, Applicants point out that the specification clearly teaches those portions of the MIST sequence that are important for the recited functional binding of MIST to Grb2, Vav, Lat, c-Cbl or SLP-76. Specifically, the specification teaches that MIST "interact[s] with signaling molecules through its SH2 domain, proline-rich motifs or its phosphotyrosine residues" (see paragraph [0156]) and provides functional data demonstrating the same in Figures 12, 13, and 14. Applicants disagree with the Examiner that the claims must contain the identification of a "particular portion of the structure that must be conserved for the biological activity of the polypeptide" since the specification clearly identifies the regions responsible for the Grb2, Vav, Lat, c-Cbl or SLP-76 binding activity. Accordingly, Applicants assert one skilled in the art would appreciate Applicants were in possession of the claimed genus, in part, based upon the recitation of the Grb2, Vav, Lat, c-Cbl or SLP-76 binding limitation since the latter requires at least one of the regions within the MIST protein responsible for such binding to be functional.

Second, Applicants point out that the instant specification explicitly discloses all N- and C-terminal deletion mutants of the MIST polypeptide (see paragraphs [0298] and [0299] on pages 100 to 105), their encoding polynucleotides, in addition to providing explicit teachings as to how one skilled in the art could actually make these mutants (see Example 10). One skilled in the art would clearly recognize that Applicants were in possession of these mutants since it would not be possible to describe the same if Applicants were not in possession of the same. Importantly, many of these sequences fall within the "at least 95%" identity limitation of Claims 47 and 48 as described *infra*.

Relative to Claim 48, the specification discloses 24 N-terminal deletion mutants, namely M1-L443 (443 amino acids in length) to T24-L443 (420 amino acids in length) of SEQ ID NO:2, that are at least 95% identical to amino acids 2 to 443 of SEQ ID NO:2 (442 amino acids in length)(e.g., 420 amino acids divided by 442 amino acids times 100 equals 95% identity). In addition, the specification also discloses 24 C-terminal deletion mutants, namely M1-L443 (443 amino acids in length) to M1-K420 (420 amino acids in length) of SEQ ID NO:2, that are at least 95% identical to amino acids 2 to 443 of SEQ ID NO:2 (442 amino acids in length)(e.g.,420 amino acids divided by 442 amino acids times 100 equals 95% identity). Applicants note that each one of these deletion mutant sequences retain at least one or more intact SH2, PR, and phosphotyrosine domains and would clearly maintain the ability to bind to Grb2, Vav, Lat, c-Cbl or SLP-76. The same argument for Claim 48 also applies to Claim 47 since nucleotides 323 to 1648 of SEQ ID NO:1 encode amino acids 2 to 443 of SEQ ID NO:2. Thus, applicants assert that the written description requirement is satisfied for both Claims 47 and 48 since more than 48 species defining the genus are explicitly disclosed which clearly constitute a representative number of species. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of Claims 47 and 48 under 35 U.S.C. § 112, first paragraph.

Applicants also disagree with the Examiner's rejection of Claims 65 to 69 and assert that the specification provides sufficient teachings to convince a skilled artisan that Applicants were in possession of a polynucleotide encoding amino acids 1 to 443 or 2 to 443 of SEQ ID NO:2 containing a "single nucleotide substitution". Specifically, the instant specification explicitly supports a polynucleotide containing such a substitution stating

> **[0050]** An allele or allelic sequence is an alternative form of the MIST nucleic acid sequence. Alleles may result from ***at least one mutation in the nucleic acid sequence*** and may yield altered mRNAs or polypeptides whose structure or function may or may not be altered. Any given gene, whether natural or recombinant, may have none, one,

> or many allelic forms. Common mutational changes which give rise to alleles are generally ascribed to natural deletions, additions, or ***substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence***. (emphasis added)

(page 13), in addition to stating the following

> **[0058]** A deletion refers to a change in either nucleotide or amino acid sequence and results in the absence of one or more nucleotides or amino acid residues. By contrast, an insertion (also termed "addition") refers to a change in a nucleotide or amino acid sequence that results in the addition of one or more nucleotides or amino acid residues, as compared with the naturally occurring molecule. ***A substitution refers to the replacement of one or more nucleotides or amino acids by different nucleotides or amino acids***. (emphasis added)

(page 16). The instant specification also teaches that such a single nucleotide substitution would encode either the same or a functionally equivalent MIST polypeptide stating

> **[0051]** ***Altered nucleic acid sequences encoding the MIST polypeptide include nucleic acid sequences containing deletions, insertions and/or substitutions of different nucleotides resulting in a polynucleotide that encodes the same or a functionally equivalent MIST polypeptide***. Altered nucleic acid sequences may further include polymorphisms of the polynucleotide encoding the MIST polypeptide; such polymorphisms may or may not be readily detectable using a particular oligonucleotide probe. The encoded protein may also contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent MIST protein of the present invention. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological activity or function of MIST protein is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid; positively charged amino acids may include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values may include leucine, isoleucine, and valine; glycine and alanine; asparagine and glutamine; serine and threonine; and phenylalanine and tyrosine. (emphasis added)

(page 13). Applicants point out that since Claim 65 is directed to a sequence containing a single nucleotide substitution of MIST, in conjunction with the fact that there are multiple domains within the MIST polypeptide, including the SH2, PR, and phosphotyrosine domains, that facilitate its binding to Grb2, Vav, Lat, c-Cbl or SLP-76, one skilled in the art would recognize that a MIST encoding polynucleotide containing a single nucleotide substitution would still maintain its ability to bind to Grb2, Vav, Lat, c-Cbl or SLP-76 on account of at least two of the domains remaining completely unaltered by definition. Applicants also remind the Examiner that it is well known in the art that SH2 and proline-rich domains are comprised of large patches of amino acids that present an

interface enabling protein-protein interactions with other proteins containing domains capable of binding to these domains. For example, the SH2 domain of MIST is comprised of 124 amino acids (see Figure 11), and the proline rich domain of MIST is comprised of 161 amino acids (see Figure 11). As a consequence, unlike enzymes that may require specific amino acids for catalytic activity, a single nucleotide substitution, regardless of whether it is conservative or non-conservative would not be expected to significantly affect the activity of these domains. Regarding the phosphotyrosine domains of MIST, Applicants point out that the specification teaches that there are at least two tyrosine residues that could be phosphorylated (see Figures 3A-B) and a single nuclelotide substitution could not affect all of the tyrosine residues by definition. Clearly, one skilled in the art would recognize that Applicants were in possession of a sequence containing a "single nucleotide substitution" based upon the teachings of the instant specification.

However, in the sole interest of facilitating prosecution, Applicants have amended Claim 65 to append the limitation ", and wherein said polynucleotide encodes a polypeptide that binds to Grb2, Vav, Lat, c-Cbl or SLP-76". Applicants believe the Examiner's rejection of Claim 65 under 35 U.S.C. § 112, first paragraph has been overcome in consideration of this amendment. In addition, since Claims 66 to 69 depend either directly or indirectly from Claim 65, Applicants believe Examiner's rejection of Claims 66 to 69 under 35 U.S.C. § 112, first paragraph has also been overcome.

c. The Examiner has rejected Claims 47 to 48, and 65 to 69 under 35 U.S.C. § 112, first paragraph, alleging these claims are not described in which a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention. More particularly, the Examiner alleges

> Claims 47-48, 65-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid encoding a polypeptide of amino acid sequence set forth in SEQ ID NO:2, does not reasonably provide enablement for an isolated nucleic acid having at least 95% sequence identity with a particnlar disclosed sequence (SEQ ID NO:l) wherein the polypeptide binds Grb2, Vav, Lat, c-Cbl or SLP-76. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.
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> Claim 47, for example, is overly broad in its limitation of "at least 95% sequence identity" because no guidance is provided as to which of the myriad of nucleic acid molecules encompassed by the claim will encode a polypeptide which

retains the characteristics of the desired polypeptide binds Grb2, Vav, Lat, c-Cbl or SLP-76. Variants of a nucleic acid can be generated by deletions, insertions, and substitutions of nucleotides, but no actual or prophetic examples on expected performance parameters of any of the possible variants of the claimed nucleic acid molecule or mutants of the protein molecule have been disclosed. Furthermore, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is no guidance provided in the instant specification as to how one of skill in the art would generate and use a nucleic acid having at least 95% sequence identity with SEQ ID NO:I (the encoded polypeptide having the biological activity of binding to Grb2, Vav, Lat, c-Cbl or SLP-76.), other than the polynucleotide of SEQ ID NO:I exemplified in the specification. See In *re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Given the breadth of the claims, in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Applicants disagree and assert that the instant specification does in fact contain the requisite teachings to enable one skilled in the art to make and use the genus encompassed by Claims 47 and 48. First, Applicants point out that Claims 47 and 48 do not merely define a genus according to sequence identity, rather, these claims also contain the functional limitation that the sequence must

bind to Grb2, Vav, Lat, c-Cbl or SLP-76. In addition, Applicants point out that the specification clearly teaches those portions of the MIST sequence that are important for the recited functional binding of MIST to Grb2, Vav, Lat, c-Cbl or SLP-76. Specifically, the specification teaches that MIST "interact[s] with signaling molecules through its SH2 domain, proline-rich motifs or its phosphotyrosine residues" (see paragraph [0156]) and provides functional data demonstrating the same in Figures 12, 13, and 14. Accordingly, Applicants assert one skilled in the art would readily be able to make and use the polynucleotides encompassed by the claimed genus of Claims 47 and 48 based, in part, upon the recitation of the Grb2, Vav, Lat, c-Cbl or SLP-76 binding limitation since the latter requires at least one of the regions within the MIST protein responsible for such binding to be functional.

Second, Applicants point out that the instant specification explicitly discloses all N- and C-terminal deletion mutants of the MIST polypeptide (see paragraphs [0298] and [0299] on pages 100 to 105), their encoding polynucleotides, in addition to providing explicit teachings as to how one skilled in the art could actually make these mutants (see Example 10). One skilled in the art would clearly would be able to make and use the sequences encompassed by Claims 47 and 48 on account of the teachings of the instant specification. Importantly, many of these sequences fall within the "at least 95%" identity limitation of Claims 47 and 48 as described *infra*.

Relative to Claim 48, the specification discloses 24 N-terminal deletion mutants, namely M1-L443 (443 amino acids in length) to T24-L443 (420 amino acids in length) of SEQ ID NO:2, that are at least 95% identical to amino acids 2 to 443 of SEQ ID NO:2 (442 amino acids in length)(e.g., 420 amino acids divided by 442 amino acids times 100 equals 95% identity). In addition, the specification also discloses 24 C-terminal deletion mutants, namely M1-L443 (443 amino acids in length) to M1-K420 (420 amino acids in length) of SEQ ID NO:2, that are at least 95% identical to amino acids 2 to 443 of SEQ ID NO:2 (442 amino acids in length)(e.g., 420 amino acids divided by 442 amino acids times 100 equals 95% identity). Applicants note that each one of these deletion mutant sequences retain at least one or more intact SH2, PR, and phosphotyrosine domains and would clearly maintain the ability to bind to Grb2, Vav, Lat, c-Cbl or SLP-76. The same argument proffered for Claim 48 also applies to Claim 47 since nucleotides 323 to 1648 of SEQ ID NO:1 encode amino acids 2 to 443 of SEQ ID NO:2.

In addition, Applicants point out that many of the deletion mutants that have been shown to have the recited Grb2, Vav, Lat, c-Cbl or SLP-76 binding activity in the instant specification, in fact, have less than 95% identity. For example, amino acids 1 to 320 of SEQ ID NO:2 shares 72%

identity with amino acids 2 to 443 of SEQ ID NO:2 (442 amino acids in length)(e.g., 320 amino acids divided by 442 amino acids multiplied by 100 equals 72%) and this fragment was shown to have Grb2 binding in Figures 12 and 13; amino acids 160 to 320 of SEQ ID NO:2 shares 36% identity with amino acids 2 to 443 of SEQ ID NO:2 (442 amino acids in length)(e.g., 161 amino acids divided by 442 amino acids multiplied by 100 equals 36%) and this fragment was shown to have Grb2 binding in Figures 12 and 13, and Cbl and Vav binding in Figure 12; amino acids 320 to 443 of SEQ ID NO:2 shares 28% identity with amino acids 2 to 443 of SEQ ID NO:2 (442 amino acids in length)(e.g., 124 amino acids divided by 442 amino acids multiplied by 100 equals 28%) and this fragment was shown to have Grb2 binding in Figures 12 and 13, Cbl and Vav binding in Figure 12, and SLP-76 binding in Figure 14. Accordingly, Applicants assert that the enablement requirement has been satisfied for both Claims 47 and 48 since more than 48 species defining the 95% identity genus are explicitly disclosed, the specification provides explicit teachings to enable one skilled in the art as to how to make (Example 10) and use these sequences (see Examples 1, 2, 3, 9, and 11), and the specification also provides data demonstrating that sequences with percent identities as low as 28% have the recited function. The same argument for Claim 48 also applies to Claim 47 since nucleotides 323 to 1648 of SEQ ID NO:1 encode amino acids 2 to 443 of SEQ ID NO:2. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of Claims 47 and 48 under 35 U.S.C. § 112, first paragraph.

Applicants also disagree with the Examiner's rejection of Claims 65 to 69 and assert that the specification also provides sufficient teachings to enable one skilled in the art to make and use a polynucleotide encoding amino acids 1 to 443 or 2 to 443 of SEQ ID NO:2 containing a "single nucleotide substitution". First, as stated *supra*, the instant specification provides explicit teachings to support a polynucleotide containing such a substitution. Secondly, Applicants pointed out *supra*, that one skilled in the art would recognize that a MIST encoding polynucleotide containing a single nucleotide substitution would still maintain its ability to bind to Grb2, Vav, Lat, c-Cbl or SLP-76 on account of at least two of the SH2, PR, and phosphotyrosine domains, domains which enable such binding, would remain completely unaltered by definition. Applicants also pointed out that the function of the SH2 and proline-rich domains is not dependent upon any single amino acid, but rather multiple amino acids and that regardless of whether a substitution was conservative or non-conservative, it would not be expected to significantly affect the activity of these domains. Regarding the phosphotyrosine domains of MIST, Applicants also point out that the specification teaches that there are at least two tyrosine residues that could be phosphorylated (see Figures 3A-B)

and a single nuclelotide substitution could not affect all of the tyrosine residues by definition. Clearly, one skilled in the art would recognize that the teachings of Applicants specification would enable them to make and use a sequence containing a "single nucleotide substitution" based upon the teachings of the instant specification.

In addition, Applicants also point out that an artisan skilled in the art of Molecular Biology already has knowledge of how to make a sequence containing a single nucleotide substitution. However, the instant specification provides teachings stating that "[s]uch variants are typically prepared by site-specific mutagenesis of nucleotides in the DNA encoding the MIST protein, using cassette or PCR mutagenesis, or other techniques that are well known and practiced in the art, to produce DNA encoding the variant." (see paragraph [0090]). In addition, the specification also teaches "[t]echniques for making substitution mutations at predetermined sites in DNA having a known sequence are well known, for example, M13 primer mutagenesis and PCR mutagenesis." (see paragraph [0091]).

However, in the sole interest of facilitating prosecution, Applicants have amended Claim 65 to append the limitation ", and wherein said polynucleotide encodes a polypeptide that binds to Grb2, Vav, Lat, c-Cbl or SLP-76". Applicants believe the Examiner's rejection of Claim 65 under 35 U.S.C. § 112, first paragraph has been overcome in consideration of this amendment. In addition, since Claims 66 to 69 depend either directly or indirectly from Claim 65, Applicants believe Examiner's rejection of Claims 66 to 69 under 35 U.S.C. § 112, first paragraph has also been overcome.

Accordingly, Applicants assert that the enablement requirement for Claims 47 to 48 and Claims 65 to 69 has been satisfied and that undue experimentation would not be required to make and use the compositions encompassed by the same since the specification enables compositions having significantly less identity than 95% in addition to sequences containing one nucleotide substitution. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of Claims 47 and 48 and Claims 65 to 69 under 35 U.S.C. § 112, first paragraph.

IV. Rejections under 35 U.S.C. § 112, second paragraph

a. The Examiner has rejected Claim 52 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner alleges

> Claim 52 is rejected as vague and indefinite because it recites "polynucleotide which represents the complete complementary sequence of (a) or (b) of Claim 36." It is unclear how the complementary nucleic acid can encode a polypeptide of amino acid sequence set forth in SEQ ID NO:2. It is suggested that a claim encompassing a complete complementary sequence of SEQ ID No:1 be written as an independent claim.

Applicants disagree and point out that Claim 52 is not directed to a complementary sequence that encodes a polypeptide – rather, Claim 52 is directed to the complementary sequence of a sequence that encodes a polypeptide. Applicants assert one skilled in the art would readily appreciate the difference between the latter based upon the double stranded (sense / antisense) nature of polynucleotides. However, in the sole interest of facilitating prosecution, Applicants have amended Claim 52 to be independent and to substitute the phrase "(a) or (b) of Claim 36" with the phrase "either an isolated polynucleotide encoding a polypeptide comprising amino acids 1 to 443 of SEQ ID NO:2, or an isolated polynucleotide encoding a polypeptide comprising amino acids 2 to 443 of SEQ ID NO:2". Applicants believe the Examiner's rejection of Claim 52 under 35 U.S.C. § 112, second paragraph has been overcome in consideration of these amendments and respectfully request that the rejection be withdrawn.

V. Rejections under 35 U.S.C. § 103(a)

a. The Examiner has rejected Claims 36 to 43, and 47 to 69 under 35 U.S.C. § 103(a), as being unpatentable over Goitsuka et al. (April 2000). More particularly, the Examiner alleges

> Goitsuka et al describes a partial isolated human MIST cDNA (see Methods, cDNA cloning and expression constructs, Figure 1). A copy of the comparison of SEQ ID NO:2 presented in the instant invention and the human MIST amino acid sequence disclosed in the reference is enclosed at the end of this action (SEQUENCE COMPARISON A). However, Goitsuka does not disclose the complete nucleic acid encoding the protein set forth in SEQ ID NO:2. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to use the cDNA disclosed by Goitsuka to screen a human cDNA library of human cord blood-derived mast cells to obtain the complete cDNA encoding human MIST and place the cDNA encoding human MIST, in an expression vector and host cell which expresses the putative protein encoded thereby, and recovering the recombinant protein produced. To have incorporated the recombinant DNA encoding the protein identified as human MIST by Goitsuka et al, into an expression vector and host cell to facilitate the production and characterization of the MIST protein encoded thereby by employing those methods that were old and well known in the art of molecular biology at the time that the instant invention was made would have been *prima facie* obvious to an artisan in light of the Goitsuka publication. Furthermore, it would have been obvious to one of ordinary skill in the art at the time that the invention was made, to

> make fragments of the cDNA encoding fragments of the human MIST protein as well as to make single nucleic acid substitutions in the human MIST cDNA to determine the relevance of the amino acids with respect to the biological activity of the protein. Therefore, the Goitsuka reference meets the limitations of claims 36-69.

Applicants disagree and assert the rejection of Claims 36 to 43, and 47 to 69 under 35 U.S.C. § 103(a) over Goitsuka et al. (April 2000) is improper. Specifically, Applicants point out that before a rejection of a claim under 35 U.S.C. § 103(a) can properly be made, each of the following must be established

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

(MPEP 2143). As recognized by the Examiner, the sequence taught by Goitsuka et al. represents a mere fragment of the claimed sequences which is clearly evidenced by the "Sequence Comparison A" alignment provided by the Examiner. As a consequence, Applicants submit that Goitsuka et al. does not satisfy the third prong of 35 U.S.C. § 103(a) since it does not "teach or suggest all the claim limitations". In addition, the Examiner has not cited any other publication that could be used, either alone or in combination with Goitsuka et al., that teaches all of the limitations of Claims 36 to 43, and 47 to 69. If fact, the Examiner acknowledges that Goitsuka et al. does not satisfy all the limitations of these claims stating "Goitsuka does not disclose the complete nucleic acid encoding the protein set forth in SEQ ID NO:2".

Relative to Claims 36, 37, 39, 41, 42, 43, and 65, the Examiner's "Sequence Comparison A" alignment adequately demonstrates that Goitsuka et al. does not disclose a sequence comprising "amino acids 1 to 443 of SEQ ID NO:2" nor "amino acids 2 to 443 of SEQ ID NO:2" nor does it disclose either of these two sequences containing a single amino acid substitution.

Relative to Claim 49, the Examiner's "Sequence Comparison A" alignment also adequately demonstrates that Goitsuka et al. does not teach the limitations of this claim since ATCC Deposit PTA-2981 contains a clone that contains the "cloned full-length MIST cDNA (i.e., clone #8)" (see paragraph [0097] on page 29) corresponding to amino acids 2 to 443 of SEQ ID NO:2.

Relative to Claims 50 and 51, the Examiner's "Sequence Comparison A" alignment also adequately demonstrates that Goitsuka et al. does not teach a "polypeptide comprising at least 352

contiguous amino acids of SEQ ID NO:2" since the Goitsuka et al. sequence contains two single amino acid mismatches at amino acids 122 and 180 which corresponds to amino acids 155 and 213 of SEQ ID NO:2. Since the Goitsuka et al. polypeptide sequence does not comprise "at least 352 contiguous amino acids of SEQ ID NO:2", the polynucleotide sequence disclosed by Goitsuka et al. cannot comprise "at least 1128 contiguous nucleotides of SEQ ID NO:1".

Relative to Claim 52, Applicants note that Goitsuka et al. does not disclose the complementary sequence of its sequence. For the reasons outlined herein, however, even if Goitsuka et al. did disclose the complementary sequence of its sequence, it would not be relevant to the complementary sequence of the polynucleotide encoding amino acids 1 to 443 of SEQ ID NO:2 nor the polynucleotide encoding amino acids 2 to 443 of SEQ ID NO:2 since the Goitsuka et al. sequence only represents a fragment of the same as evidenced by the the Examiner's "Sequence Comparison A" alignment.

Relative to Claim 53, the Examiner's "Sequence Comparison A" alignment adequately demonstrates that Goitsuka et al. does not disclose a sequence comprising "amino acid 83 to 443 of SEQ ID NO:2" since the last amino acid of the Goitsuka et al. sequence ends at amino acid 409 of SEQ ID NO:2 in addition to containing two single amino acid mismatches at amino acids 122 and 180 corresponding to amino acids 155 and 213 of SEQ ID NO:2.

Relative to Claim 55, the Examiner's "Sequence Comparison A" alignment adequately demonstrates that Goitsuka et al. does not disclose a sequence comprising "amino acids 1 to 323 of SEQ ID NO:2" since the first amino acid of the Goitsuka et al. sequence begins at amino acid 34 of SEQ ID NO:2 in addition to containing two single amino acid mismatches at amino acids 122 and 180 which corresponds to amino acids 155 and 213 of SEQ ID NO:2.

Relative to Claim 57, the Examiner's "Sequence Comparison A" alignment adequately demonstrates that Goitsuka et al. does not disclose a sequence comprising "amino acids 160 to 320 of SEQ ID NO:2" since the Goitsuka et al. sequence contains a single amino acid mismatch at amino acid 180 which corresponds to amino acid 213 of SEQ ID NO:2.

Relative to Claim 59, the Examiner's "Sequence Comparison A" alignment adequately demonstrates that Goitsuka et al. does not disclose a sequence comprising "amino acids 320 to 443 of SEQ ID NO:2" since the last amino acid of the Goitsuka et al. sequence ends at amino acid 409 of SEQ ID NO:2.

Relative to Claim 61, the Examiner's "Sequence Comparison A" alignment adequately demonstrates that Goitsuka et al. does not disclose a sequence consisting of "amino acids 324 to 407 of SEQ ID NO:2".

Relative to Claim 63, the Examiner's "Sequence Comparison A" alignment adequately demonstrates that Goitsuka et al. does not disclose a sequence comprising "amino acids 1 to 320 of SEQ ID NO:2" since the first amino acid of the Goitsuka et al. sequence begins at amino acid 34 of SEQ ID NO:2 in addition to containing two single amino acid mismatches at amino acids 122 and 180 which corresponds to amino acids 155 and 213 of SEQ ID NO:2.

Relative to Claims 38, 40, 56, and 64, Applicants bring to the attention of the Examiner the alignment provided in Exhibit A (submitted concurrently herewith) which demonstrates that Goitsuka et al. does not disclose a sequence that comprises "nucleotides 320 to 1648 of SEQ ID NO:1"; a sequence that comprises "nucleotides 323 to 1648 of SEQ ID NO:1"; a sequence that comprises "nucleotides 320 to 1288 of SEQ ID NO:1"; nor a sequence that comprises "nucleotides 320 to 1279 of SEQ ID NO:1".

Relative to Claims 54 and 58, Applicants bring to the attention of the Examiner the alignment provided in Exhibit B (submitted concurrently herewith) which demonstrates that Goitsuka et al. does not disclose a sequence that comprises "nucleotides 566 to 1648 of SEQ ID NO:1"; nor a sequence that comprises "nucleotides 797 to 1279 of SEQ ID NO:1".

Relative to Claims 60 and 62, Applicants bring to the attention of the Examiner the alignment provided in Exhibit C (submitted concurrently herewith) which demonstrates that Goitsuka et al. does not disclose a sequence that comprises "nucleotides 1277 to 1648 of SEQ ID NO:1"; nor a sequence that consists of "nucleotides 1289 to 1540 of SEQ ID NO:1".

Relative to Claim 47, Applicants bring to the attention of the Examiner Exhibit D which presents the percent identity calculations from a CLUSTALW sequence alignment between the polynucleotide sequence disclosed by Goitsuka et al. with nucleotides 323 to 1648 of SEQ ID NO:1. As shown, the Goitsuka et al. sequence shares only 85.0% identity which does not satisfy the "at least 95%" identity limitation of Claim 47.

Relative to Claim 48, Applicants also bring to the attention of the Examiner Exhibit E which presents the percent identity calculations from a CLUSTALW sequence alignment between the polypeptide sequence disclosed by Goitsuka et al. with amino acids 2 to 443 of SEQ ID NO:2. As shown, the Goitsuka et al. sequence shares only 84.6% identity which does not satisfy the "at least 95%" identity limitation of Claim 48.

Relative to Claims 66 to 69, the Examiner's "Sequence Comparison A" alignment adequately demonstrates that Goitsuka et al. does not disclose a sequence encompassed by each of Claims 36, 47, 48, 49, 50, 53, 55, 57, 59, 61, or 63.

Applicants further point out that the Federal Circuit addressed a scenario analogous to the Examiner's allegation In re Deuel (*In re Deuel*, 51 F.3d 1552, 1554-56 (Fed.Cir.1995)) and held that a partial amino acid sequence did not preclude the patentability of the full-length sequence of the HGBF cDNA despite the motivation to isolate the same and despite the high level of skill in the art to perform the isolation.

Accordingly, since Goitsuka et al. fails to teach or suggest all the claim limitations of Claims 36 to 43, and 47 to 69, the Examiner's rejection of Claims 36 to 43, and 47 to 69 under 35 U.S.C. § 103(a) is not proper and Applicants respectfully request that the Examiner withdraw the same.

b. The Examiner has rejected Claims 44, 45, and 46 under 35 U.S.C. § 103(a), as being unpatentable over Goitsuka et al. (April 2000) in view of Capon et al. patent (U.S. Patent No. 5,116,964). More particularly, the Examiner alleges

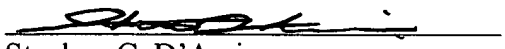
> The disclosure of Goitsuka et al has been set forth above in paragraph 5a. However, the Goitsuka et al. reference fails to disclose that the polynucleotide (encoding human MIST protein) further comprises a heterologous nucleic acid, which is the C_H region of human immunoglobulin IgG2a to increase the half-life of the MIST protein.
>
> Capon et al. teaches chimeric proteins for directing ligand binding partners such as growth factors, hormones or effector molecules to cells bearing ligands for the ligand binding partners comprising a ligand binding partner fused to a stable plasma protein which is capable of extending the in vivo half-life of the ligand binding partner when present as a fusion with the ligand binding partner, in particular wherein such a stable plasma protein is an immunoglobulin constant domain or albumin (see column 4, lines 57-64; column 5, lines 11-21 ; column 7, lines **11-27;** column 8, lines 13-15).
>
> Therefore, it would have been prima facie obvious to one having ordinary skill in the art to modify the polynucleotide of Goitsuka such that it includes a heterogenous nucleic acid sequence to obtain a chimeric protein with an increased circulating half-life, as taught by Capon et al., to obtain the known functions and advantages of the human MIST polypeptide as per the teachings of Goitsuka et al. One would have been motivated to make a chimeric nucleic acid encoding a chimeric protein comprising human MIST and human immunoglobulin to decrease its clearance rate *in vivo*. Therefore, it would have been obvious to obtain a chimeric nucleic acid encoding a chimeric protein comprising human MIST and human immunoglobulin, a long-lived molecule well known in the art as able to increase the stability of rapidly cleared molecules.

Applicants disagree with the Examiner's allegations, and assert that the rejection of Claims 44, 45, and 46 under 35 U.S.C. § 103(a) over Goitsuka et al. (April 2000) in view of Capon et al. patent (U.S. Patent No. 5,116,964) is not proper on account of Goitsuka et al. failing to teach or suggest all of the limitations of Claim 36 from which Claims 44, 45, and 46 ultimately depend. Capon et al. alone fails to teach or suggest the limitations of Claim 36. Since the Examiner's rejection of Claims 44, 45, and 46 requires the combination of Goitsuka et al. with Capon et al., combined with the fact that Capon et al. alone fails to teach or suggest the limitations of Claim 36, Applicants assert that the Examiner's rejection of Claims 44, 45, and 46 under 35 U.S.C. § 103(a) is not proper and should be withdrawn.

Applicants believe that all of the Examiners rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,



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